PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	12.04.2005
Applicant's or agent's file reference N.88110A TAC	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/001663	16.04.2004	16.04.2003

Applicant
MARGETTS, George

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference N.88110A TAC	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/001663	International filing date *(day/month/year)* 16.04.2004	Priority date *(day/month/year)* 16.04.2003
International Patent Classification (IPC) or national classification and IPC A61K31/565, A61K31/568, A61P9/00, A61P35/00, A61P11/06, A61P13/12		
Applicant MARGETTS, George		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.02.2005	12.04.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Allnutt, S Telephone No. +49 89 2399-7817

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001663

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-20	as originally filed

Claims, Numbers

1, 11-31	as originally filed
2-10	received on 16.02.2005 with letter of 15.02.2005

Drawings, Sheets

1/5-5/5	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001663

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1,5,9,28-31

   because:

   ☒ the said international application, or the said claims Nos. 29-31 (Industrial Applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1,5,9,28-31 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6,9-11,23-27
	No:	Claims	1-5,7,8,12-22,28-31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-31
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	29-31

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 29-31 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. It is not clear what exact disorders or diseases may be considered within the scope of the term "angiotensin II related disease" used in claims 1,28-31 thus rendering the definition of the subject-matter of said claim unclear, according to Article 6 PCT.
The claim can be regarded as clear only if experimental tests or testable criteria, are available from the description or from the common general knowledge allowing the skilled person to recognise which conditions fall within the functional definition and accordingly within the scope of the claim.
The modulation of the effects caused by angiotensin II cannot be considered in itself as a **real,defined** therapeutic application; the discovery that an active agent selectively interacts with a substance even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a defined, real treatment of any pathological condition in order to make a technical contribution to the art and be considered as an invention eligible for patent protection.

3. The application does not meet the requirements of Article 6 PCT, because claims 5 and 9 are not clear.
Claim 5 discloses cardiovascular diseases and includes diabetes and renal failure.
Claim 9 discloses proliferative diseases and includes peripheral arterial disease, cerebrovascular disease, cardiac myopathy, diabetic retinopathy, diabetic gangrene, diabetic nephropathy,scleroderma,aneurism and asthma.

4. The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US 2003/050291 A1 (ARAD YADON) 13 March 2003 (2003-03-13)
D2: GB-A-2 155 018 (STERWIN AG) 18 September 1985 (1985-09-18)
D3: SUZUKI GEORGE ET AL: "Effects of long-term monotherapy with eplerenone, a novel aldosterone blocker, on progression of left ventricular dysfunction and remodeling in dogs with heart failure." CIRCULATION, vol. 106, no. 23, 3 December 2002 (2002-12-03), pages 2967-2972, XP002288136 ISSN: 0009-7322

D4: YAMAKADO M ET AL: "Sites of action of beta-melanocyte stimulating hormone in aldosterone biosynthesis in the rat." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE. SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE (NEW YORK, N. Y.) JUL 1985, vol. 179, no. 3, July 1985 (1985-07), pages 318-323, XP009033422 ISSN: 0037-9727

D5: ROCHA RICARDO ET AL: "Selective aldosterone blockade prevents angiotensin II/salt-induced vascular inflammation in the rat heart." ENDOCRINOLOGY, vol. 143, no. 12, December 2002 (2002-12), pages 4828-4836, XP002288137 ISSN: 0013-7227

D6: ROUSSEAU MICHEL F ET AL: "Beneficial neurohormonal profile of spironolactone in severe congestive heart failure: Results from the RALES neurohormonal substudy." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 40, no. 9, 6 November 2002 (2002-11-06), pages 1596-1601, XP002288138 ISSN: 0735-1097

D7: LEE A F ET AL: "Neurohormonal reactivation in heart failure patients on chronic ACE inhibitor therapy: a longitudinal study." EUROPEAN JOURNAL OF HEART FAILURE : JOURNAL OF THE WORKING GROUP ON HEART FAILURE OF THE EUROPEAN SOCIETY OF CARDIOLOGY. DEC 1999, vol. 1, no. 4, December 1999 (1999-12), pages 401-406, XP002288261 ISSN: 1388-9842

D8: EP-A-0 108 606 (STERWIN AG) 16 May 1984 (1984-05-16)

The documents considered in the present processing are consecutively numbered D1-D8; this numbering results from the citations D1-D8 found in the Search Report (SR) of the corresponding PCT application. It will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

6. The technical features of claims 1-5,7,12,13,18-21 and 29 are disclosed by document D1 and therefore does not fulfill the requirements of Art 33 (2) PCT with regard to novelty. D1 discloses the use of 100-1000 mg/day of trilostane and epostane for treating insulin resistance and atherosclerosis.

The mere mechanism of action is not considered to be a technical feature being industrially applicable. It is therefore not suitable to render the subject-matter of claims novel over the cited prior art unless a new therapeutic application in terms of a real defined treatment can be shown.

7. The technical features of claims 1,2,7,8,12,13-22,28-31 are disclosed by document D2 and therefore does not fulfill the requirements of Art 33 (2) PCT with regard to novelty. D2 discloses trilostane metabolites for treating breast and prostate carcinoma.

Administration is preferably in particulate form at a unit dosage of 30-250 mg. The metabolites may be administered in combination with trilostane.

8. The remaining claims 6, 9-11, 23-27 are considered to be formally novel (Art 33(2) PCT).

Inventive Step

9. Claim 6 of the present application is not considered to involve an inventive step according to Article 33(3) PCT for the following reasons:
D1 already discloses the use of trilostane for the treatment of atherosclerosis and therefore the treatment of a further cardiovascular disease such as myocardial infarction would be an obvious step for the skilled person.

10. With respect to claims 9-11, the problem to be solved may be seen as "providing an alternative treatment for proliferative diseases including cardiofibrosis".
The solution as provided by the application is the use of steroid compound derivatives including epostane and ketostane.

D3 teaches that an aldosterone or angiotensin II inhibitor may attenuate progressive intistitial fibrosis and thus improve heart failure. It does not mention the compounds of the invention.

D4 shows that WIN19578 blocks aldosterone production and therefore it would be obvious to the skilled person to select cyanoketone or a derivative thereof for solving the problem. D2 also suggests that trilostane is useful for treating adrenal cortical hyperfunction such as primary aldosteronism (pg 3, l.1).

It is therefore noted, that the solution proposed in claims 9-11 of the present application is not considered not to satisfy the criterion set forth in Article 33(3) PCT.

The fact that examples of the invention show that the effect of trilostane is independent of aldosterone **in vivo** does not contribute to an inventive step. There is no teaching from the prior art regarding this property which would dissuade the skilled person from combining the teaching of D2 and D4 with D3 to arrive at the same solution.

11. The subject matter of claims 23-27 only involve the combination of compound of formula (I) and drugs already known to treat cardiovascular disorders (cf D5-D7). In particular D3 suggests that an ATII inhibitor and/or aldosterone inhibitor may attenuate progressive interstitial fibrosis and hence improve left ventricular diastolic function. Such a selection/combination can only be regarded as inventive, if the combination of compounds

present unexpected effects or properties in relation to other ones. This does not appear to be the case and therefore claims 23-27 are not considered as involving an inventive step (Art 33(3) PCT).

Further Remarks:

Industrial Applicability (Art 33(4) PCT).

12. For the assessment of the present claims 29-31 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.